

activity-related CNS disorders, thermoregulatory disturbances, sexual disturbances, disturbances in the cardiovascular system and [medical] disturbances in the gastrointestinal system.

16. (twice amended) A process for the manufacture of the salt as defined in claim 2 or 18 [characterized by] which comprises a final step of recrystallizing (R)-3-N,N-dicyclobutylamino-8-fluoro-3,4-dihydro-2H-benzopyran-5-carboxamide hydrogen (2R,3R)-tartrate in an appropriate aqueous organic solvent.

REMARKS

As a result of Applicants' September 17, 1998 amendment in the International Stage and their December 1, 1999 Preliminary Amendment in the National Stage, claims 1-5 and 11-19 are pending in the application. Claims 11, 12 and 16 have been further amended herein. No new matter was introduced by any of the previous amendments or by any of the amendments herein.

In the first place, Applicants would like to point out that the Examiner has not considered the proper list of claims. The list of 18 claims which was a part of the application as originally filed was replaced on September 17, 1998, while the application was still in the International Stage, with a new list of 17 claims. Since the amended list was submitted more than a year prior to the issuance of the present Office Action, said amended claims should have been part of the U.S. file and should have been the basis for the consideration of claimed subject matter in the present Office Action.

Furthermore, Applicants note that their Preliminary Amendment, submitted December 1, 1999, was not in the Examiner's possession at the time the Office Action was issued.

In any event, in view of the September 17, 1998 amendments, the claim numbering is different than that used by the Examiner in setting forth the rejections.

Original claims 8-11, now claims 7-10, were rejected under 35 U.S.C. § 101 as being nonstatutory. The cancellation of claims 7-10 in Applicants' December 1, 1999 Preliminary Amendment renders moot this rejection.

Original claims 12 and 13, now claims 11 and 12, have been rejected under 35 U.S.C. § 112, first paragraph as being nonenabled; in particular the Examiner objects to the phrases "medical disturbances" and "related medical disturbances." These claims have been amended herein to recite more particularly the subject matter regarded as the invention. As acknowledged by the Examiner, support for the claim amendments can be found on page 3, lines 6-8 of the instant specification.

Original claims 4, 7, 12, 13 and 17, now claims 3, 6, 11, 12 and 16, respectively, have been rejected under 35 U.S.C. § 112, second paragraph as being indefinite. The cancellation of claim 6 in Applicants' December 1, 1999 amendment renders moot its rejection. The Examiner has indicated that the basis for "second paragraph" rejections of claims 11 and 12 is the same as that for the "first paragraph" rejections. Accordingly, the amendments herein to claims 11 and 12 render moot the "second paragraph" rejections as well.

The Examiner has rejected original claim 17, now claim 16, because it contains the phrase "process for the manufacture of;" Applicants do not understand the basis for this rejection. The Examiner's assertion, which Applicants contend is inappropriate (see Applicants' response below to the objection to the language "crystalline form"), that the claimed salts may be assumed to be in crystalline form only is not seen to be relevant to the Examiner's stated basis for rejecting this process claim.

The rejected claim recites a method for preparing the salt of the instant invention which comprises a recrystallization step in an appropriate aqueous organic solvent. As disclosed in the instant specification on page 5, lines 18 and 19, this step can be performed in the event that a nonaqueous solvent was used in earlier steps. Furthermore, and in any event, as disclosed in the passage from page 5, line 27 to page 6, line 2, the recrystallization step is that which insures conversion of the salt in all forms to the preferred monohydrate. The claim has been amended to more clearly recite the inventive subject matter. In any case, this rejection should be withdrawn.

Original claim 4, now claims 3 and 18, has been rejected for citing the limitation "crystalline form." The Examiner asserts that the instant salts are not described as amorphous and that the instant examples are obtained only in the crystalline form and that, therefore, it can be assumed that the instant salts are in crystalline form only; again, this assumption is inappropriate.

Applicants call the Examiner's attention to, for example, page 3, lines 10-14 of the instant specification, wherein it is disclosed only that the preferred form of the salts is crystalline. It is implicit in the statement of preferred embodiment that the noncrystalline form(s) of the salt is also considered to be an embodiment of the invention.

Applicants also wish to provide further support, set forth in the example below, for the idea that the claimed invention includes both noncrystalline and crystalline forms of the salt.

(R)-3-N,N-dicyclobutylamino-8-fluoro-3,4-dihydro-2H-1-benzopyran-5-carboxamide hydrogen (2R,3R)-tartrate monohydrate (3 parts, total mass 105g) was dissolved in water (3 parts, total mass 1785g) with stirring. The solution was spray dried in 3 batches at a rate of approximately 1.5g per minute. The temperature of the drying air was set at 80°C. The measured outlet temperature varied between 55°C and 61°C during the spray drying process. The dried material from the 3 batches was combined to give 77.8g of the title substance (74% yield). The salt was found to be in amorphous form by powder x-ray diffraction ("PXRD"), and the water content thereof, determined by titration according to the method of Karl Fischer, was found to be 4.5%. The Examiner's attention is directed to the enclosed PXRD diagram showing the results of the diffraction analysis; as can be seen from the figure, the starting material, batch 103/99, was in crystalline form, and the material following spray drying, batch 2688-5, was amorphous. Applicants respectfully request

that the above information be made a part of the file record as support for the idea that the noncrystalline form of the salt is an aspect of the invention.

Applicants wish further to emphasize that, while it is true that isolation and purification is easier for salts of compounds which form crystals and that such crystalline salts can also be much less hygroscopic, the fact that these properties make such salts more desirable in general, and more suitable for pharmaceutical formulations in particular, does not preclude the use of noncrystalline forms, nor does it preclude the grant of a patent for the discovery of such forms of salts. One of ordinary skill in the art reading the instant application would understand that the salts of the instant invention comprise both forms, and Applicants are entitled to protection for both crystalline and noncrystalline forms of the inventive salt.

The pending claims have been rejected under 35 U.S.C. § 103(a) as being obvious over International Publication No. WO 95/11891 of Evenden, et al. Applicants wish to advise the Examiner that the U.S. National Stage of the cited International application issued as U.S. Patent No. 5,616,610 on April 1, 1997.

The Examiner asserts that Evenden, et al. teach a general formula which includes the present base compound and, generally, salts, including the hydrochloride and tartrate, of said base compound. The Examiner concludes that the present invention merely constitutes the "indiscriminate selection of 'some' among 'many'" and is therefore *prima facie* obvious. Again, the Examiner is in error in his assessment.

The present invention is certainly not an indiscriminate selection of some among many. Applicants have discovered a single base compound from among all of those encompassed by Evenden formula I and have further selected the tartrate salt, in particular the monohydrate, of said base compound from among the 44 salts listed in the Evenden disclosure. Applicants' surprising discovery of such a specific embodiment out of the myriad possibilities rendered by the Evenden disclosure of a multitude of compounds, and a multitude of possible salts thereof, is neither indiscriminate nor a selection of some among many. The Examiner has cited the decision of *In re Lemin*, 141 USPQ 814 in connection with this rejection. However, much more applicable cases to the present situation, wherein a specific compound within a broad genus has been discovered and there had been no motivation provided to pick that compound or any other particular compound, are *In re Ruschig*, 154 USPQ 118 and *In re Jones*, 21 USPQ2d 1941.

The Examiner alludes to the disclosure of both the hydrochloride and tartrate salts by Evenden; no distinction is made by Evenden, et al. as to the relative merits of the hydrochloride versus the tartrate or, for that matter, among any of the various salts possible. On the other hand, Applicants have tested the tartrate salt, in fact comparatively with the hydrochloride salt, and found the former to have surprising, superior properties to the latter. Reference is made to Figure 2, wherein it is shown that both the tartrate anhydrate and the preferred tartrate monohydrate salts are greatly superior to the

hydrochloride salt in their resistance to undesirable moisture uptake.

One of ordinary skill in the art certainly could not have seen that such advantageous properties would exist for a specific example from among the many possible in light of the general disclosure of Evenden, and Applicants' discovery of the superior properties of the tartrate salt certainly cannot be said to constitute discovery of something which is *prima facie* obvious over what was known at the time of filing the present application. The reasons why the specific compound according to the instant invention is patentable over the general disclosure of Evenden, et al. are equally applicable to consideration of the patentability of the instant method-of-treatment and process-for-manufacture claims.

Original claim 17, now claim 16, has been objected to under 37 C.F.R. § 1.75(c) as being an improper multiple dependent claim. Applicants' December 1, 1999 amendment of claim 16 renders moot this objection.

The Examiner has required a new title more descriptive of the claimed invention. A new title has been added by amendment herein.

In view of the above amendments and arguments, as well as the additional information provided, the subject matter recited in the pending claims is definite, enabled and patentable over the cited prior art reference. Reconsideration and allowance of pending claims 1-5 and 11-19 are respectfully requested.

The Assistant Commissioner is hereby authorized to charge any fee which may be due in connection with this communication to Deposit Account No. 23-1703.

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Respectfully submitted,

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Enclosures

Probalzotan batch 2688-5. Initial analysis

